Arguments

Priority

According to the Office Action, Applicants failed to make a proper priority claim within the time period provided in 37 CFR .78(a)(2) and (a)(5). This finding is believed to be in error. The priority information was properly provided in the Utility Patent Application Transmittal Under 37 C.F.R. § 1,53(b), accompanying the present application as filed. Indeed, the proper priority claim is reflected in the Official Filing Receipt mailed on August 8, 2001, and the updated Official Filing Receipt mailed on November 15, 2001.

Applicants note that in parallel Application No. 09/839,752, a Petition under 37 CFR 1.78(a)(3) was dismissed as moot on essentially identical facts. A copy of the decision on petition is enclosed for the Examiner's consideration. Just as in the present case, in the '752 application a reference to a prior non-provisional application was not included in an Application Data Sheet or in the first sentence of the specification following the title. Nevertheless, the priority information was provided in the transmittal letter filed with the application. According to the decision on petition: "The current procedure where a claim for priority under 37 CFR 1.78(a)(3) is not included in the first sentence of the specification or in an ADS but does appear either in the oath or declaration or a transmittal letter filed with the application and the Office notes the claim priority, no petition will be required to accept a later claim for priority."

Just as in the '752 case, in the instant case the Office noted the claim for priority of the non-provisional applications in the transmittal letter filed with the application, as shown by its inclusion on the filing receipt. Therefore, the Examiner is respectfully requested to acknowledge the claimed priorities without the need for filing a petition.

Claim Rejections - 35 USC § 112

Applicants note and appreciate the withdrawal of all claim rejections under 35 U.S.C. § 112, first paragraph for lack of written description in view of the arguments submitted in response to the previous Office Action.

Claims 13-27 (all claims pending) remain to be rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement. The Examiner states that while the teachings in Examples 2 and 3 of the specification and clinical data performed post filing "provide guidance with regard to treatment of patients suffering from vein graft failure, there is no guidance for treatment of NFκB associated diseases and conditions with NFκB decoys." The Examiner further notes that "[t]he teaching of the specification and prior art do not teach one how to make or use NFκB decoys for therapeutic purposes as neither specification nor the prior art provide the specific dosages to be administered to patients, the schedule of treatments, the specific modes of administration, the intended therapeutic targets or organs for NFκB decoy therapy." The Examiner adds that "neither the specification nor the prior art recognizes any set of diseases as being an NFκB associated diseases or conditions. . . . Therefore, the sites of administration, the intended therapeutic product and the intended target organs are unknown." With regard to the prevention aspect of the invention, the Examiner notes that "[d]isease prevention is highly unpredictable as it is unclear for whom the treatment is targeted."

Applicants respectfully disagree, and traverse the rejections.

The specification clearly teaches a set of NFκB associated diseases or conditions and provides sufficient directions for the administration of NFκB decoys

In the paragraph bridging pages 5 and 6, the specification states:

"Preferred target transcription factors [to be targeted by the decoy molecules of the invention] are activated (i.e. made available in a form capable of binding DNA) in a limited number of specifically activated cells. For example, a stimulus such as a wound, allergen, infection, etc may activate a metabolic pathway that is triggered by the transient availability of one or more transcription factors. Such transcription factors may be made available by a variety of mechanisms such as release from sequestering agents or inhibitors (e.g. NFκB bound to IκB), activation of enzymes such as kinases, translation of sequestered message, etc."

The table on page 6 specifically lists

inflammation, immune response, transplant rejection, ischemia-reperfusion injury, and glomerulonephritis

as exemplary NFκB-associated diseases and conditions.

According to the disclosure at page 10, lines 6-23 of the specification:

> The application of the subject therapeutics are preferably local, so as to be restricted to a histological site of interest e.g. localized inflammation, neoplasia or infection. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access, or the like. Where the organ or tissue is accessible because of removal from the patient, such organ or tissue may be bathed in a medium containing the subject compositions, the subject compositions may be painted onto the organ, or may be applied in any convenient way. Alternatively, systemic administration of the decoy using i.e., lipofection, liposomes with tissue targeting (e.g. antibody), etc., may be practiced. . . .
>
> Optimal treatment parameters will vary with the indication, decoy, clinical status, etc., and are generally determined empirically, using the guidance provided herein.

The table on pages 10-11 lists the following exemplary indications, and routes and vehicles for administration of NFκB decoys:

Indication	Route	Vehicle
inflammatory skin disease and dermatitis	topical	polymer
glomerulonephritis	intravenous, intrarenal	polymer, liposomes
myocardial infarction	intracoronary	liposomes, polymer
organ transplant, especially cardiac/renal	intravascular, ex vivo	liposomes, polymer

Discussion of further diseases, including prophylaxis, follows between page 11, line 13 and page 12, line 6.

These data evidence that the specification clearly teaches a set of specific NFκB-related diseases and conditions, such as those listed in the above table, and provides specific information about the sites, routes and delivery means of administration. The determination of dosages and other specific details, which depend on the actual condition targeted, is well within the skill of an ordinary artisan.

Indeed, there is scientific evidence of the involvement of NFκB in the pathogenesis in the listed and other diseases, and actual *in vivo* data confirm the efficacy of NFκB decoys in their prevention and treatment.

Evidence of the involvement of NFκB in disease pathology

It is well-established that NFκB plays a key role in the expression of several genes involved in the inflammation, cell proliferation and immune responses. (D'Acquisto *et al., Gene Therapy* 7: 1731-1737 (2000); Griesenbach *et al., Gene Therapy* 7, 306-313 (2000); Morishita *et al., Gene Therapy* 7: 1847-1852 (2000) - copies enclosed). Among the genes regulated by NFκB are many of which have critical roles in various diseases and conditions, such as rheumatoid arthritis, systemic lupus erythematosus, restenosis, myocardial infarction, ischemia reperfusion injury, glomerulonephritis, atopic dermatitis, saphenous vein graft, Alzheimer's disease, to name a few. (Khaled *et al. Clinical Immunology and Immunopathology* 86(2): 170-179 (1998); Morishita *et al., Nature Medicine* 3(8): 894-899 (1997); Cho-Chung *et al., Current Opinion in Molecular Therapeutics* 1(3): 386-392 (1999); Nakamura *et al., Gene Therapy* 9: 1221-1229 (2002); Shintani *et al., Ann. Thorac. Surg.* 74: 1132-1138 (2002); Li *et al., J. Neurochem.* 74(1): 143-150 (2000) - copies enclosed).

Furthermore, it is well known that NFκB binds to the promoter of a large number of genes involved in the inflammatory response, including intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, E-selectin (ELAM)-1, interleukin (IL)-1, tumor necrosis factor (TNF)-α, IL-8, IL-6, cyclooxygenase (COX-2) and intercellular nitric oxide synthase (iNOS). (Feeley *et al., Transplantation* 70(11): 1560-1568 (2000); Hess *et al., Stroke* 31: 1179-1186 (2000) - copies enclosed).

To illustrate this point further, it is known that the response to glomerular injury is characterized by the expression of cytokines and adhesion molecules, in particular, IL-1, IL-2, IL-6, and IL-8, and adhesion molecules, ICAM-1 and VCAM-1, are up-regulated in glomerulonephritis. (Tomita *et al., Gene Therapy* 7:1326-1332 (2000) - copy enclosed). Similarly, expression of genes, such as cytokines TNF-α and IL-1β and adhesion molecules ICAM-1, is related to ischemia-reperfusion injury (Ueno *et al., J. Thoracic and Cardiovascular Surgery* 122(4): 720-727 (2001) - copy enclosed). Further discussion of the significant role of NFκB in the coordinated transcription of cytokine and adhesion molecule genes is provided by

Morishita *et al., Nature Medicine* 3(8): 894-899 (1997); Cho-Chung *et al., Current Opinion in Molecular Therapeutics* 1(3): 386-392 (1999), copies of which are enclosed. For example, NFκB plays a pivotal role in the coordinated transactivation of cytokine and adhesion molecule genes involved in (1) atherosclerosis and lesion formation after vascular injury (Yoshimura *et al., Gene Therapy* 8: 1635-1642 (2001) - copy enclosed), (2) neuronal damage after cerebral ischemia (Ueno *et al., J. Thoracic and Cardiovascular Surgery* 122(4): 720-727 (2001) - copy enclosed), (3) chronic airway inflammation (Griesenbach *et al., Gene Therapy* 7, 306-313 (2000) - copy enclosed), (4) progression of autoimmune myocarditis (Yokoseki *et al., Circ. Res.* 89: 899-906 (2001) - copy enclosed), (5) acute rejection and graft arteriopathy in cardiac transplantation (Suzuki *et al., Gene Therapy* 7: 1847-1852 (2000) - copy enclosed), and (6) myocardial infarction (Morishita *et al., Nature Medicine* 3(8): 894-899 (1997) - copy enclosed).

This information confirms and supplements the disclosure provided in the specification about diseases and conditions associated with NFκB.

Evidence of the efficacy of NFκB decoys in the treatment and prevention of NFκB-associated diseases and conditions

Following studies in various publications further elaborate the potential prevention and treatment of NFκB associated diseases and conditions with NFκB decoy. Intimal hyperplasia develops as a result of vascular smooth muscle cell (VSMC) proliferation and migration, and it is the pathological process that underlies restenosis, atherosclerosis and vascular graft occlusion. (Yoshimura *et al., Gene Therapy* 8: 1635-1642 (2001) - copy enclosed). As mentioned above, NFκB regulates the expression of VCAM-1 and ICAM-1 as part of the inflammatory response. Yoshimura *et al.* demonstrated that *in vivo* transfection of NFκB decoy into balloon-injured rat carotid artery resulted in the inhibition of neointimal formation at 14 days after injury, and that the gene expression of ICAM-1 and VCAM-1 was markedly decreased in blood vessels transfected with NFκB decoy. (See page 1635). Therefore, Yoshimura *et al.*, showed that the NFκB decoy effectively suppressed activation of NFκB induced by balloon injury and neointimal formation. Accordingly, the authors conclude that *in vivo* transfection with NFκB decoy may provide a therapeutic strategy to *inhibit* neointimal hyperplasia after angioplasty. Similarly, the strategy may be useful in treating broad ranges of human diseases such as restenosis and

myocardial infarction. (See also Morishita *et al., Nature Medicine* 3(8): 894-899 (1997) - copy enclosed).

Suzuki *et al.,* showed that NFκB is critically involved in the development of acute and chronic rejection of the cardiac transplantation by transfecting NFκB decoy into transplanted hearts. Suzuki *et al.,* demonstrated that NFκB attenuates both acute and graft arteriopathy by blocking the coordinated transactivation of inflammatory gene expression, such as ICAM-1 and VCAM-1, involved in acute rejection. (See page 1848). Accordingly, Suzuki *et al.,* concludes that decoy treatment against NFκB provides yet another strategy for *prevention* of acute rejection and graft arteriopathy in cardiac transplantation. Similarly, NFκB decoy treatment is an effective method to block adhesion molecule expression and reperfusion injury in the immediate post-transplant period. Accordingly, the greater inhibition of reperfusion injury, acute, and chronic rejection after transplantation correspond to a prolongation of allograft survival and decrease in graft coronary artery disease. (Feeley *et al., Transplantation* 70(11): 1560-1568 (2000) - copy enclosed).

Yokoseki *et al.,* showed that NFκB is a key regulator in the progression of experimental autoimmune myocarditis (EAM), which is an autoimmune inflammatory cardiac disorder that is an animal model for human giant cell myocarditis. (See page 899). The authors introduced HVJ-liposome-DNA complex containing NFκB decoy into common carotid artery. Yokoseki *et al.* found that *in vivo* transfection of NFκB decoy with HVJ-liposome attenuates the development of EAM by effectively suppressing the inflammatory process. Accordingly, Yokoseki *et al.,* concludes that if patients with giant cell myocarditis are treated during the active phase, inflammation and *subsequent* myocardial necrosis might be suppressed, thus *in vivo* transfection of NFκB decoy provides a novel strategy for treatment of acute myocarditis. (See page 904).

Ueno *et al.,* reported that transfection of NFκB decoy blocks the transcriptional activation of cytokines and adhesion molecules to prevent ischemic reperfusion injury. Ueno *et al.,* showed that the transfected NFκB decoy effectively inhibited the expression of TNF-α, IL-1β and ICAM-1 mRNA 1 hour after global brain ischemia when the NFκB decoy was injected through the carotid artery during 20 minutes of global brain ischemia in rats. Based on its findings, Ueno *et al.* concludes that transfecting NFκB decoy into neurons would *protect* and attenuate neuronal damage after global brain ischemia. Similarly, Ueno *et al.* also reported that blocking the NFκB by NFκB decoy prevented ischemia reperfusion injury in the heart. (See pages 720-721).

Griesenbach *et al.*, demonstrated that liposome-mediated transfection with NFκB decoy significantly decreased NFκB stimulated IL-8 secretion and NFκB activation. (See page 309, right column). Therefore, Griesenbach *et al.*, showed that the secretion of the pro-inflammatory cytokine IL-8 can be attenuated by decreasing NFκB activation in a cystic fibrosis airway epithelial cell line. Accordingly, Griesenbach *et al.* concludes that NFκB is a central regulator of inflammation in the airways and other organs, and presents an attractive target for anti-inflammatory lung gene therapy.

Conclusion

The cited post-published papers do not show the use of any special techniques or approaches that are not taught in the present application or were not otherwise known in the art at the effective priority date of the present application. Accordingly, one skilled in the art at the priority date of the present application would have clearly known how to use the invention within the full scope of the claims pending, including prevention (i.e. protection and attenuation of disease conditions).

Interview Summary

Applicants express their thanks to the Examiner for the telephone interview on August 8, 2003 between the Examiner and the undersigned attorney. Applicants have noticed that the Office Action Summary marks the Office Action mailed on February 26, 2003 as "non-final," while the "Conclusion" section on page 6 seems to indicate that the action was intended to be final. During the telephone interview, the Examiner informed applicants' representative that the Office Action was intended to be final, and the "non-final" designation in the Office Action Summary is a typographical error. In view of this, applicants offered to file a Request for Continued Examination to ensure the consideration of the arguments concerning the outstanding rejections.

Based on the foregoing arguments and the submitted scientific evidence, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present invention is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should the Examiner find that there are any

further issues outstanding, she is respectfully invited to contact the undersigned attorney in order to arrange a personal interview.

The Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.:39753-0021C3). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 11, 2003

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